ID/2004/043

सत्यमेव जयते

INTELLECTUAL PROPERTY INDIA

GOVERNMENT OF INDIA
MINISTRY OF COMMERCE & INDUSTRY
PATENT OFFICE, DELHI BRANCH
W - 5, WEST PATEL NAGAR
NEW DELHI - 110 008.

I, the undersigned being an officer duly authorized in accordance with the provision of the Patent Act, 1970 hereby certify that annexed hereto is the true copy of the ***Application, Provisional Specification*** *and* ***Drawing Sheets*** *filed in connection with Application for Patent No.* ***950/Del/2003*** *dated* ***31st July 2003.***

Witness my hand this 16th day of November 2004.

(S.K. PANGASA)
Assistant Controller of Patents & Designs

PRIORITY DOCUMENT
SUBMITTED OR TRANSMITTED IN COMPLIANCE WITH RULE 17.1(a) OR (b)

461K31/55
A61K31/35
A61K45/55

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31 JUL 2003

FORM 1

THE PATENTS ACT, 1970
(39 of 1970)

New Delhi
Received Rs. 3080/- in cash.
Cheque/M.O /I.P.O./D.D.
on 31 JUL 2003
Vide Entry No. 5045 in the
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A. O .....Cashier

APPLICATION FOR GRANT OF A PATENT

(See Sections 5(2), 7, 54 and 135; and rule 39)

1 We, **RANBAXY LABORATORIES LIMITED**, a Company incorporated under the Companies Act, 1956, Corporate Office at 19, Nehru Place, New Delhi - 110 019, India

2. hereby declare –

(a) that we are in possession of an invention titled **"AN IMPROVED PROCESS FOR PREPARATION OF HIGHLY PURE BENAZEPRIL"**.

(b) that the Provisional Specification relating to this invention is filed with this application.

(c) that there is no lawful ground of objection to the grant of a patent to us.

3. Further declare that the inventors for the said invention are

a. YATENDRA KUMAR

b. SWARGAM SATHYANARAYANA

c. SHANTANU DE

d. MOHAMMED RAFEEQ

of Ranbaxy Laboratories Limited, Plot No. 20, Sector-18, Udyog Vihar Industrial Area, Gurgaon – 122001 (Haryana), India, all Indian Nationals.

4. We claim the priority from the application(s) filed in convention countries, particulars of which are as follows: **NOT APPLICABLE**

5. We state that the said invention is an improvement in or modification of the invention, the particulars of which are as follows and of which we are the applicant: **NOT APPLICABLE**

6. We state that the application is divided out of our application, the particulars of which are given below and pray that this application deemed to have been filed on ..... Under section 16 of the Act. **NOT APPLICABLE**

7. That we are the assignee or legal representatives of the true and first inventors.

8. That our address for service in India is as follows:

DR. B. VIJAYARAGHAVAN
Associate Director – Intellectual Property
Ranbaxy Laboratories Limited
Plot No.20, Sector – 18, Udyog Vihar Industrial Area,
Gurgaon – 122001 (Haryana). INDIA.

9. Following declaration was given by the inventors or applicants in the convention country:
We, YATENDRA KUMAR, SWARGAM SATHYANARAYANA, SHANTANU DE, MOHAMMED RAFEEQ of Ranbaxy Laboratories Limited, Plot No. 20, Sector – 18, Udyog Vihar Industrial Area, Gurgaon–122001 (Haryana), India, all Indian Nationals, the true and first inventors for this invention or applicant in the convention country declare that the applicant herein, **Ranbaxy Laboratories Limited**, Corporate Office at 19, Nehru Place, New Delhi - 110 019, India, is our assignee or legal representatives.

a.

(YATENDRA KUMAR)

b.

(SWARGAM SATHYANARAYANA)

c.

(SHANTANU DE)

d.

(MOHAMMED RAFEEQ)

10. That to the best of our knowledge, information and belief the fact and matters stated herein are correct and that there is no lawful ground of objection to the grant of patent to us on this application.

11. Followings are the attachment with the application:
   a. Provisional Specification (3 copies)
   b. Drawings (3 copies)
   c. Priority document(s)
   d. Statement and Undertaking on FORM – 3
   e. Power of Authority (Not required)
   f. Fee Rs.**3,000/-** (Rupees Three Thousand only..) in cheque bearing No. dated : drawn on **HDFC Bank Limited, New Delhi.**

We request that a patent may be granted to us for the said invention.

Dated this **31ST** day of **July, 2003.**

For Ranbaxy Laboratories Limited

(SUSHIL KUMAR PATAWARI)
Company Secretary

FORM 2 DEL 03

The Patents Act, 1970 31 MAY 2005
(39 of 1970)

PROVISIONAL SPECIFICATION
(See Section 10)

AN IMPROVED PROCESS FOR PREPARATION OF HIGHLY PURE BENAZEPRIL

RANBAXY LABORATORIES LIMITED
19, NEHRU PLACE, NEW DELHI - 110019
(A Company incorporated under the Companies Act, 1956)

The following specification particularly describes and ascertains the nature of this invention and the manner in which it is to be performed:

The present invention relates to an improved process for preparation of highly pure benazepril of Formula I as shown in the accompanied drawing or pharmacologically acceptable salt thereof by completely eliminating the impurity of 7-bromo analogue of benazepril of Formula Ia as shown in the accompanied drawing.

Benazepril is chemically (3S)-1-(carboxymethyl)-[[(1S)-1-(ethoxycarbonyl)-3-phenylpropyl] amino]-2,3,4,5-tetrahydro-1H-[1]benzazepin-2-one of Formula I as shown in the accompanied drawing. It is a well-known long acting angiotensin converting enzyme (ACE) inhibitor primarily used for the treatment of hypertension. Benazepril was reported for the first time in US Patent No. 4,410,520.

The two key intermediates in the preparation of benazepril are, 3-(S)-amino-1-carboxymethyl-2,3,4,5-tetrahydro-1H-[1]benzazepin-2-one or its 1-carboxymethyl protected derivatives of Formula II as shown in the accompanied drawing and ethyl (R)-2-hydroxy-4-phenylbutyrate or its activated analogues of Formula III as shown in the accompanied drawing. These two intermediates are condensed in presence of a base to get Benazepril.

Our pending Indian patent application 374/DEL/2001 describes an improved process for preparation of benazepril. Trifluoromethane sulphonic ester of ethyl (R)-2-hydroxy-4-phenylbutyrate of Formula III is condensed with 1-t-butoxycarbonylmethyl-3-(S)-amino-2,3,4,5-tertrahydro-1H-[1]benzazepin-2-one (herein onwards referred as 3-(S)-amino t-butyl ester) of Formula II as shown in the accompanied drawing in presence of methylene chloride and N-methyl morpholine followed by treatment of crude oil obtained with dry hydrogen chloride gas to give benazepril hydrochloride of Formula Ib as shown in the accompanied drawing.

Even though the process described in the above said patent application starts with the key intermediate of Formula II, the purity of the said key intermediate is of great concern. An impurity of 7-bromo-1-t-butoxycarbonylmethyl-3-(S)-amino-2,3,4,5-tetrahydro-1H-[1]benzazepin-2-one (herein onwards referred as 7-bromo-3-(S)-amino impurity) of Formula IIa is present in it between 3 to 8%. The purification of the said intermediate is therefore required which results in loss of valuable yield. If the said intermediate of Formula II is used as such without purification to remove 7-bromo-3-(S)-amino impurity in the preparation of benazepril a corresponding impurity of 7-bromo analogue of benazepril hydrochloride of Formula Ia is obtained between 2 to 5%. Removal of this impurity from final product is very difficult requiring several purification stages, which results in lower yield.

US Patent No. 4,575,503 discloses the synthesis of benazepril. The process described produces benazepril in less yield. Further the presence of 7-bromo-3-(S)-amino impurity of Formula IIa and 7-bromo analogue of benazepril of Formula Ia and its removal from the product is not discussed in this patent. US Patent No. 4,692,522 provides benzofused lactams which are CCK antagonists wherein preparation of intermediate 3-(S)-amino t-butyl ester of Formula II is disclosed. The process however, does not disclose the synthesis of benazepril or pharmaceutically acceptable salts thereof using the said intermediate of Formula II. Also the quantities of raw materials described are significantly high.

One of the embodiments of the specification provides an improved process for preparation of highly pure benazepril of Formula I or its physiologically acceptable salts of Formula Ib, which is devoid of 7-bromo benazepril of Formula Ia. This is achieved by using pure 3-(S)-amino t-butyl ester of Formula II as shown in the accompanied drawing, which in turn is devoid of 7-bromo-3-(S)-amino t-butyl ester impurity of Formula IIa.

According to another embodiment, the 7-bromo-3-amino t-butyl ester impurity of Formula IIa is removed from the key intermediate 3-(S)-amino t-butyl ester of Formula II by reductive dehalo-hydrogenation using noble metal catalyst in presence of hydrogen or source of hydrogen. The said 3-(S)-amino t-butyl ester of Formula II, which does not contain any detectable quantity of 7-bromo-3-amino impurity, is treated with trifluoromethane sulphonic ester of ethyl (R)-2-hydroxy-4-phenylbutyrate of Formula III in presence of a base to get highly pure benazepril of Formula I. which is then converted, to its physiologically accepted salts of Formula Ib. Thus according to this embodiment the 3-azido t-butyl ester of Formula IV containing about 3 to 8% of the 7-bromo-3-azido impurity of Formula IVa, as shown in the accompanied drawing, is hydrogenated in presence of Raney nickel in methanol to get racemic 3-amino t-butyl ester of Formula V containing 7-bromo-3-amino t-butyl ester impurity of Formula Va, which after dehalo-hydrogenation over palladium on carbon in methanol gave pure racemic 3-amino t-butyl ester, wherein the corresponding 7-bromo-3-amino t-butyl ester impurity is not only removed but also converted to the desired 3-amino t-butyl ester.

According to still another embodiment, the 3-azido t-butyl ester of Formula IV containing the 7-bromo-3-azido impurity of Formula IVa up to 8% is hydrogenated over palladium on carbon to get pure racemic 3-amino t-butyl ester of Formula V wherein the corresponding 7-bromo-3-amino t-butyl ester impurity of Formula Va is absent. In this process two changes are achieved in a single reaction. Firstly, the 3-azido groups present in the starting material as well as in the

impurity are reduced to 3-amino group and secondly the 7-bromo group present in the impurity is cleaved. In fact, the 7-bromo-3-azido impurity after subjecting it to hydrogenation over palladium on carbon gives the desired racemic 3-amino t-butyl ester product.

Racemic 3-amino t-butyl ester after resolution with tartaric acid followed by hydrolysis of corresponding 3-(S)-amino t-butyl ester tartarate salt of Formula VI gives 3-(S)-amino t-butyl ester of Formula II which is used as such in the synthesis of benazepril as discussed above. The embodiments of the specification provide product with improved quality, superior yield and commercial acceptability. Benazepril obtained by following the process of the embodiments is devoid of 7-bromo benazepril impurity. Also, the yield of benazepril is increased as the yield of 3-(S)-amino t-butyl ester of Formula II is further increased during the hydrogenation with palladium on carbon where even the undesired 7-bromo-3-azido impurity of Formula IVa is not only removed but also converted to the required intermediate.

A still yet another embodiment of the specification provides an improved process for preparation of highly pure benazepril of Formula I, as shown in the accompanied drawing, or a pharmaceutically acceptable salt thereof of Formula Ib as shown in the accompanied drawing, wherein the said process comprises of following steps:

a) hydrogenating the 3-azido t-butyl ester of Formula IV of the accompanied drawing, optionally containing 7-bromo-3-azido impurity of Formula IVa, in presence of a metal catalyst and isolating the racemic 3-amino t-butyl ester of Formula V which is optionally devoid of the corresponding 7-bromo-3-amino impurity of Formula Va.

b) hydrogenating the 3-amino t-butyl ester of Formula V of the accompanied drawing, optionally containing 7-bromo-3-amino impurity of Formula Va, in presence of a noble metal catalyst and isolating the 3-amino t-butyl ester of Formula V.

c) converting the racemic 3-amino t-butyl ester of Formula V to the pure 3-(S)-amine t-butyl ester tartarate salt of Formula VI.

d) hydrolysis of the tartarate salt of Formula VI to get 3-(S)-amine t-butyl ester of Formula II.

e) condensing the 3-(S)-amine t-butyl ester obtained in step c) with trifluoromethane sulphonic ester of ethyl (R)-2-hydroxy-4-phenylbutyrate of Formula III as shown in the accompanied drawing to get t-butyl ester of benazepril of Formula Ic.

f) converting t-butyl ester of benazepril of Formula Ic to highly pure benazepril of Formula I which can be optionally converted to its physiologically accepted salt of Formula Ib and its solvates or hydrates.

The starting material 3-azido t-butyl ester of Formula IV as shown in Scheme 1 of the accompanied drawing can be prepared using method described by Blicke et al., J. Am. Chem. Soc.. 76. 2317 (1954). Brenner et al., Helv. Chem. Acta, 41, 181 (1958) and Green et al., Protecting Groups in Organic synthesis, John Willey and Sons, New York (1998). The 7-bromo-3-azido impurity of Formula IVa is present in this up to 8%. The purification of this intermediate is not carried out but it was directly subjected to hydrogenation.

The hydrogenation at step (a) is performed using a metal catalyst, which may be selected from palladium on carbon, platinum oxide, platinum black, palladium acetate, rhodium on carbon or Raney nickel. The palladium on carbon catalyst is commercially available in several strengths ranging from 1 to 10% of palladium adsorbed on carbon. The source of hydrogen can be hydrogen gas or compounds, which generate hydrogen gas when used in hydrogenation. The source of hydrogen can be selected from a group comprising ammonium formate, formic acid, alkali metal formats such as sodium formate, potassium formate. When such compounds are used as source of hydrogen the reaction can be carried out at atmospheric pressure and at a lower temperature. Organic solvent used in the step (a) can be selected from alkanols, esters and cyclic ethers or mixtures thereof. The alkanols include methanol, ethanol, propanol and isopropanol or mixtures thereof. The temperature range of hydrogenation reaction can be between 10 to 60°C.

The hydrogenation in step b) can be optional. It can be performed when hydrogenation in step a) is performed with Raney nickel. When step a) is performed using palladium on carbon as metal catalyst, step b) can be omitted. The metal catalysts used in this step can be selected from a group comprising of palladium on carbon, platinum oxide, platinum black, palladium acetate, rhodium on carbon. The other conditions such as source of hydrogen, solvent and reaction temperature are similar to that mentioned above for step a) or can be modified based on the variations therein.

Racemic mixtures of prochiral amines are converted to their diastereomeric salts by treating them with chirally active organic acids known to a person skilled in the art. The mixture of diastereomers is then separated by suitable means such as crystallization or chromatography. The required diastereomer salt is then converted back to the chiral amine by treating it with a base. The salt formation at step (c) is performed to get the desired 3-(S)-amino t-butyl ester intermediate of Formula II. Organic acid used is chirally active L-(+)-tartaric acid. The organic solvent used in the salt formation can be selected from alkanol, ester, ether and ketone or a mixture thereof. The alkanol can be selected from a group consisting of methanol, ethanol,

propanol and isopropanol or mixtures thereof. Seeding the reaction mixture with pure 3-(S) - amino t-butyl ester tartarate salt followed by cooling can effect the crystallization of the pure 3-(S)-amino t-butyl ester tartarate salt of Formula VI.

In step (d), the 3-(S)-amine tartarate salt of Formula VI is hydrolysed to generate the free 3-(S)-amine t-butyl ester of Formula II. This is achieved by treating the above said salt with a base in presence of water or an organic solvent selected from polar protic or polar aprotic solvents. The pH of the reaction mass after addition of the base can be adjusted to about 7.5 to 12. The base used can be an inorganic base such as sodium or potassium hydroxide, sodium or potassium carbonate, sodium or potassium bicarbonate. Ammonia or ammonium hydroxide can also be used as bases. The organic bases such as triethylamine, diisopropylamine, and cyclohexylamine can be used. Preferably ammonium hydroxide is used as base. The product is then extracted in the suitable organic solvent known to a person skilled in the art such as methylene chloride or chloroform and the solvent was removed by vacuum distillation. The residue can then be isolated from the residue by addition of another solvent, which is selected from a group comprising of diethyl ether, diisopropyl ether, cyclohexane, hexane and heptane or mixtures thereof.

The intermediate trifluoromethane sulphonic ester of ethyl (R)-2-hydroxy-4-phenylbutyrate of Formula III was prepared by method described in our pending Indian patent application 374/DEL/2001.

The condensation in step (e) is performed in presence of a base. The organic solvent for condensation is selected from a group comprising haloalkanes such as chloroform, carbon tetrachloride, methylene chloride, ethylene bromide and ethylene chloride or mixtures thereof. The base used can be selected from a group comprising pyridine and its derivatives, morpholine and its derivatives, trialkyl amines and cyclic amines or mixtures thereof.

The physiologically acceptable salt of benazepril of Formula Ib, can be prepared by treating benazepril t-butyl ester of Formula Ic with an acid in an organic solvent. The protecting t-butyl group is removed along with salt formation during this treatment. The acid can be hydrochloric acid used as a gas and purged through the solution of benazepril base in an organic solvent or can be a solution of hydrogen chloride gas in an organic solvent. The organic solvent can be alkanol such as methanol, ethanol, isopropanol or ester such as ethyl acetate, ethyl formate, isopropyl acetate or ketone such as acetone, or ether such as diethyl ether, diisopropyl ether,

tetrahydrofuran or mixtures thereof. The crude benazepril obtained is subjected to solvent crystallization. The solvents for crystallization include alkanol such as methanol, ethanol, propanol and isopropanol or esters such as ethyl acetate, ethyl formate, butyl acetate or ketones such as acetone, ethyl methyl ketone, methyl isobutyl ketone, diisobutyl ketone or mixtures thereof.

In a still another embodiment, 3-azido compound of Formula IV containing corresponding 7-bromo impurity of Formula IVa is hydrogenated over 10% palladium on carbon in methanol using ammonium formate as hydrogen source at 25 to 40°C to get racemic 3-amino compound of Formula V in which the corresponding 7-bromo impurity is not detectable. The racemic 3-amino compound is treated with L-(+)-tartaric acid and the tartarate salt mixture was crystallized from ethanol to get (S)-tartarate salt of Formula VI which is then hydrolysed to generate 3-(S)-amine of Formula II at a pH of 9 to 9.2 adjusted using ammonium hydroxide in a mixture of water and methylene chloride. The said 3-(S)-amine compound is then reacted with trifluoromethane sulphonic ester of ethyl (R)-2-hydroxy-4-phenylbutyrate of Formula III in methylene chloride at room temperature in methylene chloride using N-methyl morpholine as base. The product t-butyl ester of benazepril of Formula Ic is dissolved in ethyl acetate and treated with hydrochloric acid gas to get benazepril hydrochloride of Formula Ib which is then purified from methanol and ethyl acetate mixture to get highly pure Ib in which corresponding 7-bromo impurity of Formula Ia or its hydrochloride salt is not detectable.

In the following examples, the preferred embodiments of the present invention are described only by way of illustrating the process of the invention. However, these are not intended to limit the scope of the present invention any way.

EXAMPLES

Preparation of (3S)-1-(carboxymethyl)-[[(1S)-1-(ethoxycarbonyl)-3-phenylpropyl]amino]-2,3,4,5-tetrahydro-1H-[1]benzazepin-2-one hydrochloride (Benazepril hydrochloride of Formula Ib)

Step A (using 10% palladium on carbon as metal catalyst)

Preparation of (±) 1-t-butoxycarbonylmethyl-3-amino-2,3,4,5-tetrahydro-1H-[1]benzazepin-2-one ((±) 3-amino t-butyl ester, Formula V)

To a solution of 1-t-butoxycarbonylmethyl-3-azido-2,3,4,5-tertrahydro-1H-[1]benzazepin-2-one (5 g, 15.8 mmol) of Formula IV containing 1-t-butoxycarbonylmethyl-7-bromo-3-azido-2.3.4.5-tetrahydro-1H-[1]benzazepin -2-one of Formula IVa as impurity (7.67%) in methanol (25 ml) was added 10% palladium on carbon (0.5 g, 50% wet). The mixture was stirred at room temperature under hydrogen gas at a pressure of 40 to 50 psi with periodic venting. After 16 hours the reaction mass was filtered through celite bed to remove palladium on carbon and the filtrate was concentrated to dryness under vacuum to provide the title product as viscous oil which solidified on keeping

Yield: 4.5 g, 98%

Purity: 87.47%

7-Bromo-3-amino t-butyl ester impurity: Not detected.

Alternatively Step A can be performed using ammonium formate as source of hydrogen

Preparation of (±) 1-t-butoxycarbonylmethyl-3-amino-2,3,4,5-tetrahydro-1H-[1]benzazepin-2-one. ((±) 3-amino t-butyl ester, Formula V)

To a solution of 1-t-butoxycarbonylmethyl-3-azido-2,3,4,5-tetrahydro-1H-[1]benzazepin-2-one (5 g, 15.8 mmol) of Formula IV containing 1-t-butoxycarbonylmethyl-7-bromo-3-azido-2,3,4,5-tetrahydro-1H-[1]benzazepin -2-one of Formula IVa as impurity (7.67%) in methanol (25 ml) containing palladium on carbon catalyst (0.5 g, 10%, 50% wet) was added ammonium formate (10.0 g, 15.75 mmol). The temperature of the reaction mass was slowly raised to 40-50°C and stirred at this temperature for 16 hours. After confirming the reaction completion by TLC, the catalyst was removed by filtration and the filtrate was concentrated under vacuum and the residue was dissolved in methylene chloride (50 ml) and water (50 ml). The organic layer was separated and solvent removed under vacuum to get the title product as amorphous solid.

Yield: 4.55 g, 99%

Purity: 89.88%

7-Bromo-3-amino t-butyl ester impurity: Not detected.

Step A (Using Raney nickel as metal catalyst)

Preparation of (±) 1-t-butoxycarbonylmethyl-3-amino-2,3,4,5-tetrahydro-1H-[1]benzazepin-2-one. ((±) 3-amino t-butyl ester, Formula V)

To a solution of 1-t-butoxycarbonylmethyl-3-azido-2,3,4,5-tetrahydro-1H-[1]benzazepin-2-one (5 g, 15.8 mmol) of Formula IV containing 1-t-butoxycarbonylmethyl-7-bromo-3-azido-2,3,4,5-tetrahydro-1H-[1]benzazepin -2-one of Formula IVa as impurity (7.67%) in methanol (25 ml) was added Raney nickel (0.82 g). The mixture was stirred at 50-55°C under hydrogen gas at a pressure of 40 to 50 psi with periodic venting. After 16 hours the reaction mass was filtered through celite bed to remove Raney nickel and the filtrate was concentrated to dryness under vacuum to provide the title product as viscous oil which solidified on keeping.

Yield: 4.5 g, 98%

Purity: 87.47%

7-Bromo-3-amino t-butyl ester impurity: 5.28%.

Step B

Preparation of (±) 1-t-butoxycarbonylmethyl-3-amino-2,3,4,5-tetrahydro-1H-[1]benzazepin-2-one. ((±) 3-amino t-butyl ester, Formula V)

To a solution of 1-t-butoxycarbonylmethyl-3-amino-2,3,4,5-tetrahydro-1H-[1]benzazepin-2-one (5 g, 17.24 mmol) of Formula V containing 1-t-butoxycarbonylmethyl-7-bromo-3-amino-2,3,4,5-tetrahydro-1H-[1]benzazepin-2-one of Formula Va as impurity (5.28%) in methanol (25 ml) was added 10% palladium on carbon (0.5 g, 50% wet) and ammonium formate (10 g, 15.75 mmol). The mixture was stirred at room temperature. After 12 hours the reaction mass was filtered through celite bed to remove palladium on carbon and the filtrate was concentrated to dryness under vacuum to provide the title product as viscous oil. The oil obtained was further treated with dichloromethane (50 ml) and water (50 ml). The organic layer was cautiously treated with diluted sodium bicarbonate solution and solvent removed in vacuuo to give a residue which was further crystallized in ether to get the desired title compound

Yield: 4.75 g, 98%

Purity: 95%

7-Bromo-3-amino t-butyl ester impurity: Not detected.

Step C

Preparation of tartarate salt of 1-t-butoxycarbonylmethyl-3-(S)-amino-2,3,4,5-tetra hydro-1H-[1]benzazepin-2-one (tartarate salt of 3(S)-amino t-butyl ester, Formula VI)

(±) 3-amino t-butyl ester of Formula V (5.0 g, 17.24 mmol) was heated in ethanol (12.5 ml) at 50-55°C for 25 minutes. The temperature was further raised to 60-65°C and to this was added a solution of L-(+)-tartaric acid (1.8 g, 11.9 mmol) in ethanol (7.5 ml). The reaction mixture was stirred for 24 hours at 60-65°C, allowed to cool to 35-37°C and filtered at the same temperature to afford the crude product (2.75 g, 72%). This was suspended in alcohol (11 ml) and stirred at 62-65°C for 3 hours, allowed to cool to 45-47°C and filtered to afford the title compound.

Yield: 2.55 g, 93%

Purity: 99.87%.

Step D

Preparation of 1-t-butoxycarbonylmethyl-3-(S)-amino-2,3,4,5-tetrahydro -1H-[1]benzazepin-2-one (3(S)-amino t-butyl ester, Formula II)

To a suspension of 3-(S)-amino-1-t-butoxycarbonylmethyl-2.3.4.5-tetrahydro-1H[1]-benzazepin-2-one tartarate salt of Formula VI (5.0 g, 11.36 mmol) in water (50 ml) gradually added ammonium hydroxide (~ 5 ml) drop-wise till the pH is about 9.0 to 9.2. The solution was stirred and to it added methylene chloride (12.5 ml). The reaction mixture was stirred for further 30 minutes and the layers were separated. The solvent was concentrated under vacuum to get residue, which was crystallized from ether to get title compound.

Yield: 2.6 g, 80%

Purity: 99.88%

7-Bromo-3(S)-amino t-butyl ester impurity: Not detected.

Step E

Preparation of (3S)-1-(t-butoxycarbonylmethyl-[[(1S)-1-(ethoxycarbonyl)-3-phenyl propyl]amino]-2,3,4,5-tetrahydro-1H-[1]benzazepin-2-one hydrochloride (Benazepril t-butyl ester, Formula Ic)

To a solution of trifluoromethane sulphonic ester of ethyl (R)-2-hydroxy-4-phenylbutyrate of Formula III in 15 ml of methylene chloride was added a solution of 5.67 gm of 3(S)-amine t-butyl ester of Formula II and 2.46 gm of N-methyl morpholine in methylene chloride drop-wise at room temperature. The reaction mixture was stirred for 2 hours. The completion of the reaction was monitored by HPLC. The reaction was quenched by addition of 40 ml of water and 60 ml of methylene chloride. The pH adjusted to 8.5 with 10% sodium bicarbonate solution. The

organic layer was separated and washed twice with water. It was then dried over anhydrous sodium sulphate and solvent was distilled off to afford title compound as an oily residue.

Step F

Preparation of (3S)-1-(carboxymethyl)-[[(1S)-1-(ethoxycarbonyl)-3-phenylpropyl]amino]-2,3,4,5-tetrahydro-1H-[1]benzazepin-2-one hydrochloride (Benazepril hydrochloride of Formula Ib)

To a solution of benazepril t-butyl ester of Formula Ic in ethyl acetate cooled to about 10 to 12°C purged dry hydrogen chloride gas slowly without allowing the temperature to rise. The salt formation was monitored by TLC and after completion of reaction excess hydrogen chloride and solvent was completely removed under vacuum. To the residue added, 45 ml acetone and the resultant mixture was stirred for 1 hour at 5-8°C. The product was filtered and dried to constant weight under vacuum at 45-50°C affording 8.27 gm of almost white product with diastereoisomer ratio of SS:SR = 99.36:0.18. Yield 91.6%.

The product obtained was dissolved in methanol and treated with activated charcoal. The solution was filtered through celite bed to remove charcoal and then concentrated under vacuum to recover methanol to get a oily residue. Ethyl acetate was added to this residue drop-wise till slight haziness starts. Seeded the hazy solution with pure benazepril hydrochloride and stirred. Added more ethyl acetate drop-wise and cooled to about 5-10°C. Stirred for further 5 hours and then filtered the separated product. The slurry of wet product was stirred in ethyl acetate. Filtered the product and dried in vacuum oven at 45-50°C to get highly pure benazepril hydrochloride of Formula Ib.

Yield: 8.27 g, 91.9%

Diastereoisomer ratio of SS : SR = 99.36 : 0.18.

Purity: 99.75%

7-Bromo analogue of Benazepril: Not detected.

Dated 31ST day of **July, 2003.**

For Ranbaxy Laboratories Limited

(Sushil Kumar Patawari)
Company Secretary

ABSTRACT

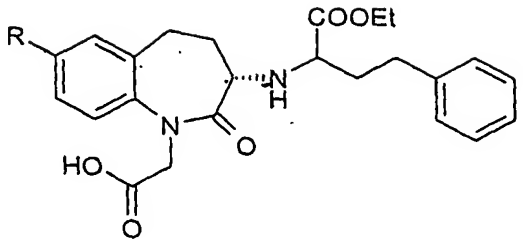
The present invention relates to an improved process for preparation of highly pure benazepril which comprises hydrogenating 3-azido t-butyl ester optionally containing 7-bromo-3-azido impurity in presence of a noble metal catalyst followed by resolution of the 3-amino t-butyl ester product with L-(+)-tartaric acid to pure 3(S)-amine t-butyl ester tartarate salt which in turn hydrolysed in presence of a base to generate 3(S)-amine t-butyl ester devoid of the 7-bromo-3-amino impurity. The product 3(S)-amine t-butyl ester is reacted with trifluoromethane sulphonic ester of ethyl(R)-2-hydroxy-4-phenylbutyrate in presence of a base to get highly pure benazepril devoid of 7-bromo benazepril isomer which is then converted to its physiologically accepted salts.

Ranbaxy Laboratories Limited

Application No.

No. of sheets = 07

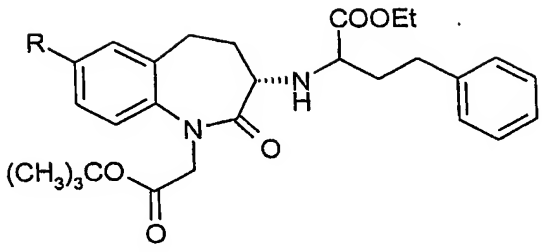
Sheet 01 of 07



I (R=H)
Ia (R=Br)
Ib (R=H). HCl

For Ranbaxy Laboratories Limited

(Sushil Kumar Patawari)
Company Secretary



Ic (R=H)
Id (R=Br)

For Ranbaxy Laboratories Limited

(Sushil Kumar Patawari)
Company Secretary

Ranbaxy Laboratories Limited

Application No.

No. of sheets = 07

Sheet 03 of 07

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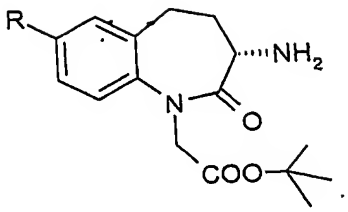
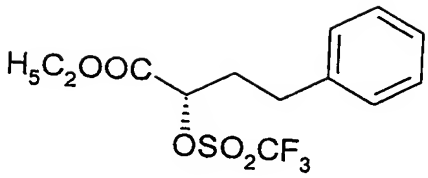


II (R=H)
IIa (R=Br)

For Ranbaxy Laboratories Limited

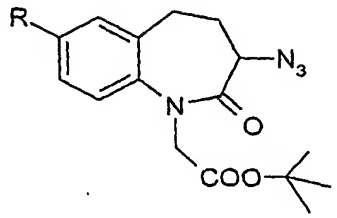
(Sushil Kumar Patawari)
Company Secretary



III

For Ranbaxy Laboratories Limited

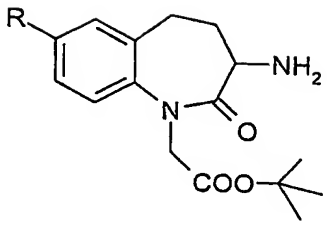
(Sushil Kumar Patawari)
Company Secretary



IV (R=H)
IVa (R=Br)

For Ranbaxy Laboratories Limited

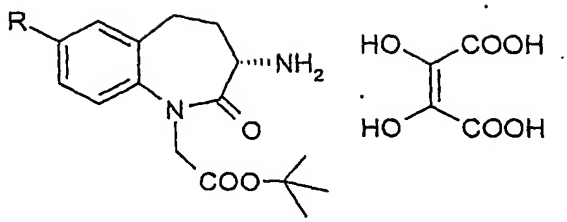
(Sushil Kumar Patawari)
Company Secretary



V (R=H)
Va (R=Br)

For Ranbaxy Laboratories Limited

(Sushil Kumar Patawari)
Company Secretary



VI (R=H)
VIa (R=Br)

For Ranbaxy Laboratories Limited

(Sushil Kumar Patawari)
Company Secretary